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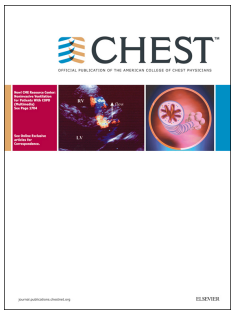
DOI:
10.1378/chest.15-1622

License:
Unspecified

Document Version
Peer reviewed version

Citation for published version (Harvard):
Fauchier, L, Lecoq, C, Clementy, N, Bernard, A, Angoulvant, D, Ivanes, F, Babuty, D & Lip, GY 2016, 'Oral anticoagulation and the risk of stroke or death in patients with atrial fibrillation and one additional stroke risk factor: the Loire Valley Atrial Fibrillation Project', *Chest*, vol. 149, no. 4, pp. 960-968. https://doi.org/10.1378/chest.15-1622

Accepted Manuscript



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Laurent Fauchier, MD, Coralie Lecoq, MD, Nicolas Clementy, MD, Anne Bernard, MD, Denis Angoulvant, MD, Fabrice Ivanes, MD, Dominique Babuty, MD, Gregory YH. Lip, MD

PII: S0012-3692(15)00027-6

DOI: 10.1378/chest.15-1622

Reference: CHEST 26

To appear in: *CHEST*

Received Date: 6 July 2015

Revised Date: 6 August 2015

Accepted Date: 2 September 2015

Please cite this article as: Fauchier L, Lecoq C, Clementy N, Bernard A, Angoulvant D, Ivanes F, Babuty D, Lip GY, Oral anticoagulation and the risk of stroke or death in patients with atrial fibrillation and one additional stroke risk factor: the Loire Valley Atrial Fibrillation Project, *CHEST* (2015), doi: 10.1378/chest.15-1622.

Oral anticoagulation and the risk of stroke or death in patients with atrial fibrillation and one additional stroke risk factor: the Loire Valley Atrial Fibrillation Project

Running title: Oral anticoagulation and atrial fibrillation.

Laurent Fauchier, MD[1], Coralie Lecoq, MD[1], Nicolas Clementy, MD[1], Anne Bernard, MD[1], Denis Angoulvant, MD[1], Fabrice Ivanes, MD[1], Dominique Babuty, MD[1], Gregory YH Lip, MD[2,3].

Affiliations:

[1]Service de Cardiologie, Centre Hospitalier Universitaire Trousseau et Faculté de Médecine, Université François Rabelais, Tours, France

[2] University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham B18 7QH, United Kingdom; and Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark.

Disclosures

This study has received no financial or material support.

DA has received funding for conference travel and educational symposia from Astra Zeneca, Eli-Lilly, Novartis, Bayer, MSD, Amgen, Pfizer. DB has been on the speakers bureau from BMS/Pfizer and Medtronic. GYHL has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi Aventis, Biotronik, BMS/Pfizer, and Boehringher Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringher Ingelheim, and Sanofi Aventis. LF has served as a consultant for Bayer, BMS/Pfizer, Boehringer Ingelheim, Medtronic and Novartis and has been on the speakers bureau from Bayer, BMS/Pfizer, Boehringher Ingelheim, Boston Scientific and Medtronic. Other authors - no conflicts of interest.

Author contributions :

Dr Fauchier and Lecoq made the primary contribution to data collection. Dr Fauchier and Dr Lip contributed to the study conception and design. Dr Fauchier and Lecoq performed the

analyses and produced the initial manuscript. All authors contributed to interpretation of results, revising the manuscript critically for important intellectual content, and all approved the final manuscript.

Drs Fauchier and Lip are guarantors of the paper.

Corresponding authors :

Laurent Fauchier, lfau@med.univ-tours.fr

Gregory Y H Lip, g.y.h.lip@bham.ac.uk

ABSTRACT

Background It remains uncertain whether patients with atrial fibrillation (AF) and a single additional stroke risk factor (CHA_2DS_2-VASc score = 1 in males, 2 in females) should be treated with oral anticoagulation (OAC). We investigated the risk of ischemic stroke, systemic embolism and death in a community-based cohort of unselected AF patients with a 0-1 stroke risk factors, based on the CHA_2DS_2-VASc score.

Methods Among 8962 patients with AF seen between 2000 and 2010, 2177 (24%) had 0 or 1 additional stroke risk factor, of which 53% were prescribed OAC.

Results Over a follow-up of 979±1158 days, 151 (7%) had a major adverse event (stroke/systemic thromboembolism/death). Prescription of OAC was not associated with a better prognosis for stroke/systemic thromboembolism/death for 'low risk' patients (ie. CHA_2DS_2-VASc score = 0 for men or 1 for women) [adjusted Hazard Ratio(HR) 0.68, 95% CI 0.35-1.31, p=0.25]. OAC use was independently associated with a better prognosis in AF patients with a single additional stroke risk factor (ie. CHA_2DS_2-VASc score = 1 in males, 2 in females) [adjusted HR 0.59, 95% CI 0.40-0.86, p=0.007].

Conclusion Among AF patients with one single additional stroke risk factor (CHA_2DS_2-VASc score = 1 in males, 2 in females), OAC use was associated with an improved prognosis for stroke/systemic thromboembolism/death.

Keywords: Atrial fibrillation; oral anticoagulant; CHA_2DS_2-VASc score

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia, and confers a substantial risk of fatal and disabling stroke. Randomized trials for patients with AF have conclusively demonstrated that compared to placebo, oral anticoagulation (OAC) reduces the risk of stroke/systemic embolism by 64% *and* all cause mortality by 26% [1].

Despite the five-fold excess risk of stroke with AF, this risk is not homogeneous and depends on the presence of various risk factors. These risk factors have been used to formulate various stroke risk stratification schemes. Current European and the ACC/AHA/HRS guidelines recommend use of the CHA_2DS_2VASc score, but the approach is different in different guidelines [2–4].

The 2014 AHA/ACC/HRS guidelines recommend a categorical approach to stroke risk assessment, and treatment decisions based on whether patients are low, moderate or high risk. For those with a CHA_2DS_2VASc score ≥2, OAC is recommended, whilst for those with a CHA_2DS_2VASc score 0, no antithrombotic therapy is recommended. However, for those with a CHA_2DS_2VASc score 1, the recommendation is for 'no antithrombotic therapy, aspirin or OAC' (Class IIb, level of evidence C) [4]. In contrast, the ESC and NICE guidelines recommend the initial step is to identify 'low risk' patients (ie. CHA_2DS_2VASc score 0 for males, 1 for females) who do not need any antithrombotic therapy. The subsequent step is to offer effective stroke prevention (ie. OAC) to patients with ≥1 stroke risk factors [3,5].

The aim of this study was to study the impact of OAC use on stroke/systemic embolism/death in patients with AF and one single additional stroke risk factor (that is, CHA_2DS_2-VASc score = 1 in males, 2 in females), compared with that of low risk patients (CHA_2DS_2-VASc score = 0, or 1 in females), Second, we investigated the relative contribution to stroke/systemic embolism/death or the various risk factor components of the CHA_2DS_2-VASc score.

METHODS

Study population

The detailed methods and design of the Loire Valley AF Project has previously been reported [6–8]. We included all patients seen in the cardiology department at the University Hospital of Tours between January 2000 and December 2010 with a diagnosis of AF, and identified patients who were categorised as low risk (CHA_2DS_2-VASc score = 0, or 1 in females) and those with one single additional stroke risk factor (ie. CHA_2DS_2-VASc score = 1 in males, 2 in females).

AF (paroxysmal, persistent or permanent) was defined on the electrocardiogram by the replacement of consistent P waves by rapid oscillations or fibrillatory waves that vary in amplitude, shape, and timing, associated with an irregular, frequently rapid ventricular response when atrioventricular conduction was intact. Treatment at discharge was obtained by the screening of hospitalization reports. Patients were excluded from the study if their antithrombotic treatment at discharge was unknown. We also excluded from the analysis patients with a known mitral stenosis or any valvular prosthesis in whom OAC was theoretically indicated. Characteristics of the patients were obtained by the coding system filled in for each patient hospitalized through the computerized system of the institution, based on the international classification of diseases (ICD-10) (supplementary table 1). With these characteristics, the CHA_2DS_2-VASc score could be calculated retrospectively as previously described [2]: 2 points assigned for a history of stroke/transient ischemic attack/thromboembolism and age $\geq$ 75 years; 1 point assigned for age 65-74 years, history of hypertension, diabetes, recent cardiac failure, vascular disease (myocardial infarction, complex aortic plaque, and peripheral arterial disease), and female gender.

During the follow-up of the patients, deaths from all causes and strokes were recorded whenever they occurred in our institution, which includes a total of 4 hospitals covering all medical and surgical specialties. Our hospital covers an area of 4000 km^2, and a population of 400.000 inhabitants and is the only public institution in the area. In addition, mortality data were obtained using a search tool from the website of the main regional newspaper of the Région Centre, 'La Nouvelle République' (http://nrco.lanouvellerepublique.fr/dossiers/necro/index.php).

In this 'real world' registry, some deaths could be due to undiagnosed stroke, as cerebral imaging or post mortems were not mandated, unlike a clinical trial. Also, OAC use reduces the risk of stroke/systemic embolism *and* all-cause mortality. Thus, the primary adverse endpoint for this study was the composite of 'stroke/systemic embolism/death'. Severe bleeding was defined as a decrease in the blood haemoglobin level of more than 5.0 g/dL (including the period around the coronary interventional procedure), the need for transfusion of one or more unit of blood, the need for corrective surgery, the occurrence of an intracranial or retroperitoneal haemorrhage, or any combination of these events. A secondary adverse endpoint for this study was the composite of 'stroke/systemic embolism/death and major bleeding'.

Statistical analysis

Patient characteristics are reported as percentages and the mean ± standard deviation (SD). Comparisons between groups were made using chi-square tests for comparing categorical variables and the Student t test or non-parametric Kruskal Wallis test were appropriate for continuous variables. In order to identify independent characteristics associated with the occurrence of an event (stroke or death) during the follow-up, a multivariate analysis was performed and potential confounders were entered into a Cox model for adjustment. A

Kaplan-Meier survival analysis with the log-rank test was carried out. A Cox proportional hazards regression model was used to calculate the hazard ratio (HR) of some predictive factors and their 95% confidence interval (CI) for the incidence of death/stroke or systemic thromboembolism. The proportional hazard assumption was checked by plotting the log-log Kaplan Meier curves. A p-value < 0.05 was considered statistically significant. Statistical analysis was carried out with the Statview 5.0 software (Abacus Concepts, Berkley, CA, USA).

Ethics approval

The study was approved by the institutional review board of the Pole Coeur Thorax Vaisseaux from the Trousseau University Hospital (Tours, France) on December 7, 2010 and registered as a clinical audit. Ethical review was therefore not required. Patient consent was not sought. Patient data were utilized only to facilitate the cross referencing of data sources and records were otherwise anonymous. The study was conducted retrospectively, patients were not involved in its conduct, and there was no impact on their care.

RESULTS

From 8962 unselected and consecutive patients with AF seen between 2000 and 2010, there were 2177 (24%) with 0 or 1 single additional stroke risk factors (CHA_2DS_2-VASc score = 0 or 1 in males, 1 or 2 in females). Mean age was 55±14 and 662 (30%) were female. Figure 1 shows repartition of the risk factors and the percentage of OAC use for the different criteria in the study population. OAC use was lower for patients with no additional risk factor (CHA_2DS_2-VASc score = 0, or 1 in females) and those with a history of vascular disease, and higher for those with a history of heart failure, hypertension, diabetes and those age ≥65 years. Baseline characteristics of the patients with AF and 0 or 1 single additional stroke risk factor are shown in Table 1. Patients treated with OAC were older and more likely to be male and more frequently had heart failure, hypertension, valvular disease, a history of chronic pulmonary disease, permanent AF and an implantable device. During follow-up, patients with no OAC were more often treated with an antiplatelet agent (44% vs. 7%, $p<0.0001$) whereas those with an OAC were more often treated using ACE inhibitors or angiotensin 2-blockers, beta-blockers and diuretics.

During a follow-up of 979±1158 days, 151 events of the primary endpoint (death, stroke or systemic thromboembolism) were recorded in AF patients with 0 or 1 single additional risk factor. In addition, 30 patients had a major bleeding and 163 patients had events of the secondary endpoint. Figure 2 shows the population sorted in 6 groups (5 components of the score, except female gender, and CHA_2DS_2-VASc score of 0). Low risk patients (CHA_2DS_2-VASc score =0, or 1 in females) had the lowest event rate compared to other groups ($p<0.0001$). No significant differences were found between the 5 other groups ($p=0.34$). The comparison for the occurrence of stroke/systemic embolism/death in AF patients with 0 or 1 single additional risk factor (CHA_2DS_2-VASc score = 0 or 1 in males, 1 or 2 in females)

according to gender and shows no significant difference between females and males (p=0.15), even after adjustment for age (HR = 0.72, p=0.08) (figure2) .

When comparing the occurrence of stroke/systemic embolism/death' in patients with *no additional stroke risk factor* (ie. CHA_2DS_2-VASc score = 0, or 1 in females) treated with OAC vs those treated with no OAC there was no advantage with OAC use (p=0.67), even after adjustment for age and gender (HR=0.68, p=0.25) (figure 3). In patients with *one single additional risk factor* (ie. CHA_2DS_2-VASc score =1 in males, 2 in females), patients treated with OAC had a lower risk of stroke/systemic embolism/death (p=0.01), and the lower risk persisted even after adjustment on age and gender (HR= 0.59, p=0.007) (Figure 3).

Figure 4 illustrates the rate of events in AF patients with a CHA_2DS_2-VASc score of 1 (male with 1 additional risk factor or female with 0 additional risk factor) treated with OAC according to ESC guidelines (no OAC for female, OAC for male) versus patients treated in a different way. Patients treated with OAC as proposed by the ESC guidelines had a lower rate of events of the primary and of the secondary endpoints and the results were still significant after adjustment for age and gender.

The different presumed risk factors for stroke/systemic embolism/death were analysed by univariate and multivariate analysis (Table 2). Older age, heart failure, chronic pulmonary disease, kidney disease and the lack of OAC treatment were independently associated with a higher risk of events. OAC use was independently associated with a 45% decrease in the occurrence of events. Table 3 indicates the hazards ratios for stroke/systemic embolism/death in patients with AF with 1 single additional stroke risk factor. Compared to patients with no

risk factor, hazard ratio of events with one single additional risk factor ranged from 1.48 for hypertension to 3.04 for heart failure and was statistically significant for patients with heart failure and those age ≥65 years.

As a sensitivity analysis, our results were similar even when use of beta-blocker and/or ACE inhibitor was added in the multivariable Cox models for the endpoints presented in table 2 (death, stroke or systemic TE) and table 5 (death, stroke/TE or major bleeding) [full data not shown].

DISCUSSION

In this cohort study, our principal finding was that among AF patients with one single additional stroke risk factor (CHA_2DS_2-VASc score = 1 in males, 2 in females), OAC use was associated with an improved prognosis for stroke/systemic thromboembolism/death. Oral anticoagulation was not associated with a better prognosis in patients in the 'low risk' category (CHA_2DS_2-VASc score = 0, or 1 in females). Overall, this supports the strategy for OAC proposed in the current European and NICE guidelines. Adding major bleeding in the combined endpoint of our analysis led to similar findings.

Our data are consistent with a recent Danish registry analysis and the Taiwanese national insurance study, where AF patients with a single risk factor had an ischaemic stroke risk of >1.5%/year and >2.5%/year, respectively [9,10]. In contrast, one recent study from Sweden suggested that the previous estimate of the risk of ischemic stroke in AF patients with one risk factor may be <1% but this study excluded any patient started on OAC during follow-up, thus 'conditioning for the future' since higher risk subjects would have been excluded [11].

As with Chao et al. [12], which was a study conducted in an Asian/non-European patient population, the present study shows that the effects of factors which contribute to a CHA_2DS_2-VASc score of 1 did not vary significantly. However, in an initial validation cohort for the CHA_2DS_2-VASc score in Denmark, the relative risk of ischemic stroke associated with the 6 risk factors leading to a CHA_2DS_2-VASc score of 1 varied significantly and was up to 5 times greater between the highest (diabetes) and lowest risk (vascular disease) [9]. Huang et al. [13] found that among the risk factors, hypertension created the highest risk, followed by age and female gender, and there was no statistically significant increase in ischemic strokes among AF patients with a history of heart failure, diabetes or vascular disease other than strokes. By contrast, Healey et al. did not find that a history of hypertension was an independent high risk factor of stroke in the ACTIVE-W trial [14]. The influence of hypertension on prognosis may have changed over recent years due to a more efficient management of hypertension in patients and better blood pressure control[15]. Vascular disease has also been determined as an independent risk factor of stroke in AF patients [16]. This was particularly apparent especially when Asian individuals were compared to Europeans [17].

Our analysis where female and male patients were considered together may suffer from a lack of power for some subgroups. Overall, we did not find significant differences in relative hazard between each criteria of the score (gender excepted) in our series of unselected and well characterized AF patients, and we suggest that patients with one additional stroke risk factor have a relatively homogeneous increased risk, although a history of heart failure may be more impacted. Of note, all point estimates were >1.0 (ranging from 1.48 to 3.04) but small sample size led to some confidence intervals crossing neutral.

Female gender has been consistently demonstrated to be an independent risk factor for

ischemic stroke among patients with AF[18-20]. In the 2012 focused update of the ESC guidelines for management of AF, the recommendation is that female AF patients aged <65 and without any additional risk factor are at a low risk of ischemic stroke and should not be prescribed antithrombotic therapy. In our study, we cannot conclude that female AF patients with a CHA_2DS_2-VASc of 1 have a higher risk of ischemic stroke than their male counterparts as found by Huang et al. As the mean age of our patients with CHA_2DS_2-VASc score of 1 was 61 years, many would be >65 years after 40 months of follow-up. Any increase in the risk of ischemic stroke at this time would likely also be related to increasing age, not female gender alone, consistent with the suggestion that female gender would be a stroke risk modifier rather than a risk factor *per se*.

In our study, there was no benefit for OAC in reducing the occurrences of stroke/systemic thromboembolism/death in AF patients with no additional stroke risk factor (CHA_2DS_2-VASc score = 0, or 1 in females). By contrast, OAC treatment was associated with a clear benefit when compared with no OAC treated patients when one additional stroke risk factor was present (CHA_2DS_2-VASc score = 1 in males, 2 in females). Chao et al.[12] support recommending OAC for all AF patients except those at a very low stroke risk (as identified by a CHA_2DS_2-VASc score of 0 or 1 for women) and our findings corroborate these conclusions and the 2012 ESC guidelines. In contrast, the ACC/AHA/HRS guidelines recommend no antithrombotic therapy or treatment with either OAC or aspirin for CHA_2DS_2-VASc score=1, in other words: “do what you like", but our findings do not support this strategy. The trials with non-vitamin K antagonist oral anticoagulant agents (NOACs) also provide data for benefit even with a single risk factor albeit with using the $CHADS_2$ score. Thus, physicians should appreciate that even a single risk factor confers real risks of stroke/systemic thromboembolism/death, and OAC would reduce this overall risk.

Limitations

The main limitation of this study is in its observational nature. Although it was adjusted for several variables, some patients might have higher acuity of illness and it is still possible that residual confounding factors between the groups could have been omitted in the analysis. The distribution of medications differed between groups, and the observational method, even after multivariate adjustment, raises a question as to whether some groups were merely managed better with a possible treatment bias, particularly those with OAC use. However, the inclusion criteria noticeably made the population relatively homogeneous. Due to the hospital based nature of the cohort, the absolute risk of death or stroke was higher than that of previous population-based series[18-20]. This may be because such patients tend to be sicker than those in a community-based cohort. While we carefully ascertained all strokes and intracranial haemorrhage through examination and hospitalization records, laboratory and imaging results, patients with a milder form of stroke and/or intracranial haemorrhage who were not hospitalized may have not been seen in hospital. Studies with a long-term follow-up as this one are often at risk of changes in treatment during the follow-up, which is impossible to make adjustments for in the multivariable analysis. Quality of anticoagulation with time in therapeutic range was not available. Another caveat is that we did not have access to data on strokes occurring outside of our area. If a resident moved from the area and had stroke diagnosed elsewhere, information on the event was unavailable to us.

However, we rather see the ability to report nonrandomized, real-world registry data from a large cohort of consecutive patients recruited as an advantage, not a weakness, in that the data are *complementary (and supportive)* to the data reported in randomized, clinical trials. In fact, a large randomized control trial addressing the issues presented here will probably not be performed soon. Observational studies such as ours may be of value because they shed light

on the use of competing treatment options in current practices and because they include patients with a higher risk profile who are frequently not represented in clinical trials.

CONCLUSION

In a real life cohort study, among AF patients with one single additional stroke risk factor (CHA_2DS_2-VASc score = 1 in males, 2 in females), OAC use was associated with an improved prognosis for stroke/systemic thromboembolism/death.

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LEGENDS TO FIGURES

Figure 1. Flow chart of patients with non valvular AF and low risk of stroke (CHA_2DS_2-VASc score 0, or 1 in females) or with 1 additional risk factor (CHA_2DS_2-VASc score 1 in males, 2 in females)

Figure 2.

Top panel : Comparison of occurrence of primary endpoint (death, stroke or systemic thromboembolism) in AF patients with low risk of stroke (CHA_2DS_2-VASc score 0, or 1 in females) or with 1 additional risk factor (CHA_2DS_2-VASc score 1 in males, 2 in females)

Lower panel: Comparison of occurrence of primary endpoint (death, stroke or systemic thromboembolism) in AF patients with low risk of stroke (CHA_2DS_2-VASc score 0, or 1 in females) or with 1 additional risk factor (CHA_2DS_2-VASc score 1 in males, 2 in females) according to male or female gender

Figure 3.

Top panel: Comparison of occurrence of primary endpoint (death, stroke or systemic thromboembolism) in AF patients with low risk of stroke (CHA_2DS_2-VASc score 0, or 1 in females) according to therapy with OAC or no OAC

Lower panel: Comparison of occurrence of primary endpoint (death, stroke or systemic thromboembolism) in AF patients with 1 additional risk factor (CHA_2DS_2-VASc score 1 in males, 2 in females) according to therapy with OAC or no OAC

Figure 4. Comparison of occurrence of primary endpoint (death, stroke or systemic thromboembolism, top panel) or secondary endpoint (death, stroke, systemic thromboembolism or major bleeding, lower panel) in AF patients with CHA_2DS_2-VASc score 1 (male with 1 additional risk factor or female with 0 additional risk factor) treated in accordance with OAC according to ESC guidelines versus others patients

TABLE 1. BASELINE CHARACTERISTICS OF THE POPULATION OF AF PATIENTS WITH LOW RISK OF STROKE (CHA_2DS_2-VASC SCORE 0, OR 1 IN FEMALES) OR WITH 1 ADDITIONAL RISK FACTOR (CHA_2DS_2-VASC SCORE 1 IN MALES, 2 IN FEMALES) ACCORDING TO THERAPY WITH OAC OR NO OAC

	Patients treated with no oral anticoagulant (n=956)	**Patient treated with oral anticoagulant (n=1053)**	**p**
Age (years) (mean±SD)	50±15	58±11	<0.0001
Male gender	615 (64%)	786 (77%)	<0.0001
Permanent atrial fibrillation	126 (13%)	425 (40%)	<0.0001
Heart Failure	120 (13%)	213 (20%)	<0.0001
Hypertension	42 (4%)	75 (7%)	0.009
Diabetes mellitus	14 (1%)	21 (2%)	0.36
Vascular diseases	30 (3%)	23 (2%)	0.18
Coronary artery disease	92 (10%)	109 (10%)	0.59
Previous myocardial infarction	22 (2%)	16 (2%)	0.19
Previous CABG	9 (1%)	15 (1%)	0.32
Previous PCI	39 (4%)	27 (3%)	0.06
Valvular disease	65 (7%)	112 (11%)	0.002
Thyroid disorder	51 (5%)	57 (5%)	0.94
Alcohol abuse	37 (4%)	45 (4%)	0.65
Renal insufficiency	13 (1%)	13 (1%)	0.80
Pacemaker or ICD	65 (7%)	117 (11%)	0.0008
Chronic pulmonary disease	43 (4%)	77 (7%)	0.008
Medication during follow-up			
Antiplatelet agent	416 (44%)	73 (7%)	<0.0001
Angiotensin converting enzyme inhibitor or Angiotensin 2-blocker	102 (11%)	286 (28%)	<0.0001
Beta blocker	330 (35%)	477 (46%)	<0.0001
Diuretic	72 (8%)	175 (20%)	<0.0001

CABG = coronary artery bypass grafting, ICD = implantable cardioverter defibrillator, PCI = percutaneous coronary intervention

TABLE 2. UNIVARIATE AND MULTIVARIATE ANALYSIS OF PRIMARY ENDPOINT (DEATH, STROKE OR SYSTEMIC THROMBOEMBOLISM) PREDICTORS IN THE POPULATION OF AF PATIENTS WITH LOW RISK OF STROKE (CHA_2DS_2-VASC SCORE 0, OR 1 IN FEMALES) OR WITH 1 ADDITIONAL RISK FACTOR (CHA_2DS_2-VASC SCORE 1 IN MALES, 2 IN FEMALES)

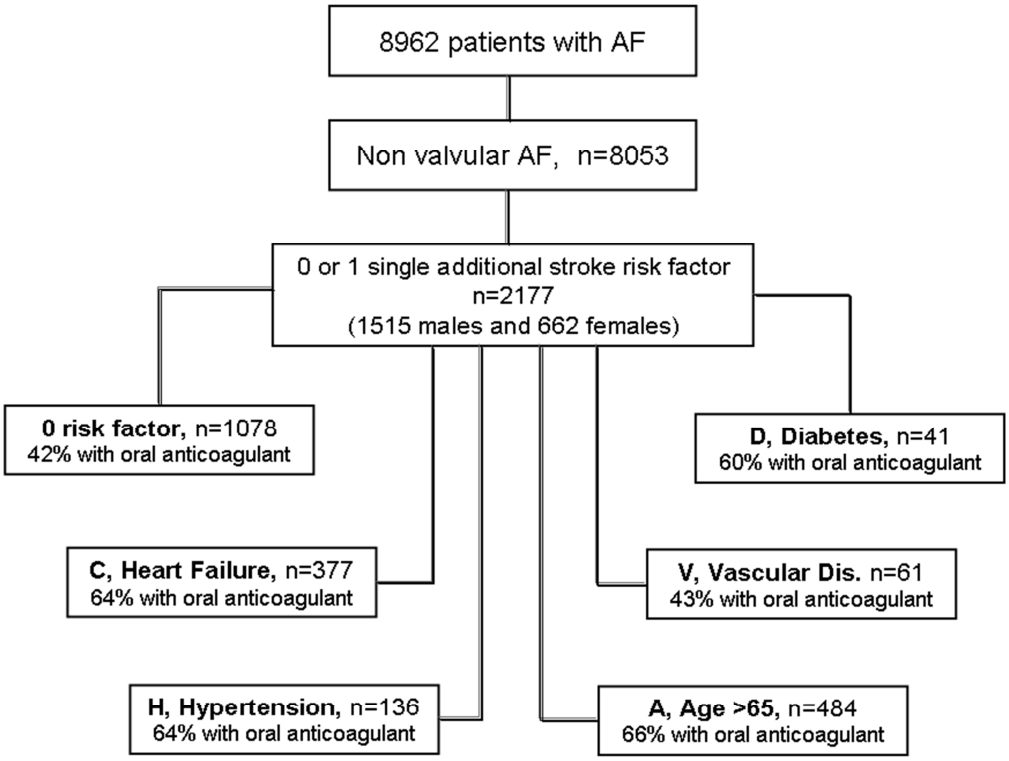
	Univariate analysis		**Multivariate analysis**	
	Hazard Ratio (95% Confidence Interval)	**p**	**Hazard Ratio (95% Confidence Interval)**	**p**
Age	1.05 (1.03-1.06)	<0.0001	1.06 (1.04-1.08)	<0.0001
Female gender	0.77 (0.53-1.11)	0.16	0.72 (0.48-1.08)	0.12
Heart Failure	2.04 (1.45-2.86)	<0.0001	2.99 (1.95-4.57)	<0.0001
Hypertension	0.81 (0.41-1.59)	0.55	1.40 (0.66-2.95)	0.38
Diabetes	1.25 (0.40-3.85)	0.71	2.75 (0.85-8.93)	0.09
Vascular disease	1.18 (0.55-2.50)	0.67	1.36 (0.55-3.33)	0.50
Coronary artery disease	1.45 (0.93-2.27)	0.10	1.22 (0.71-2.10)	0.48
Valvular disease	2.04 (1.37-3.03)	0.0004	1.56 (1.01-2.41)	0.05
Renal insufficiency	5.26 (2.63-10.0)	<0.0001	4.55 (2.16-9.52)	<0.0001
Chronic pulmonary disease	2.04 (1.23-3.33)	0.01	1.94 (1.15-3.28)	0.01
Permanent atrial fibrillation	1.10 (0.78-1.54)	0.60	0.94 (0.65-1.36)	0.73
Oral anticoagulant treatment	0.83 (0.60-1.15)	0.25	0.55 (0.38-0.80)	0.002
Antiplatelet treatment	1.03 (0.70-1.52)	0.88	0.80 (0.52-1.23)	0.31

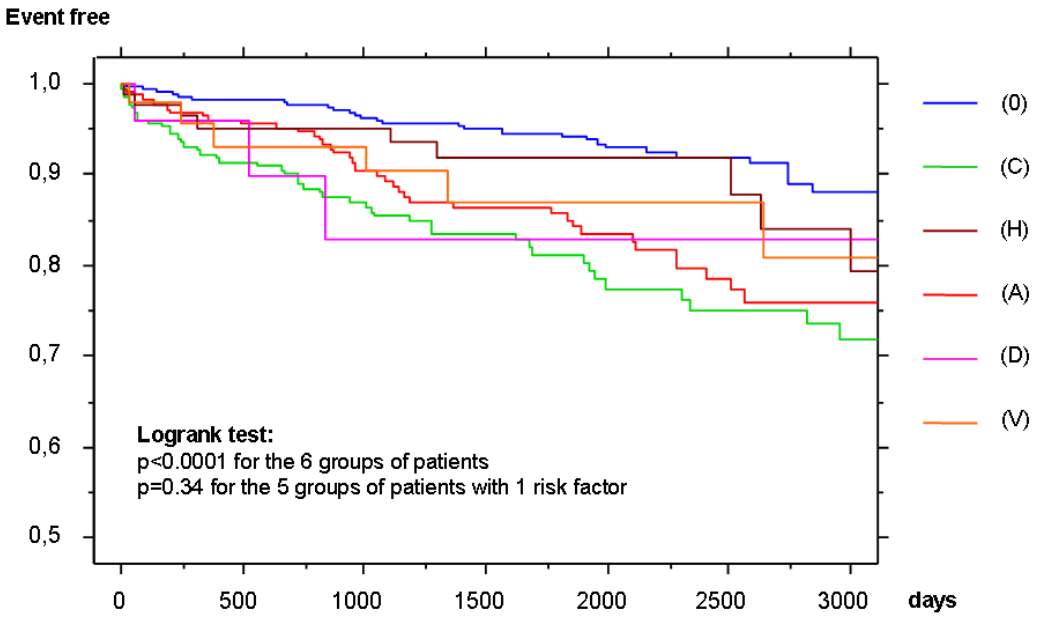
TABLE 3 .HAZARD RATIO FORPRIMARY ENDPOINT (DEATH, STROKE OR SYSTEMIC THROMBOEMBOLISM) PREDICTORS IN PATIENTS WITH ATRIAL FIBRILLATION WITH 1 ADDITIONAL RISK FACTOR (CHA_2DS_2-VASC SCORE 1 IN MALES, 2 IN FEMALES) COMPARED TO THE POPULATION OF AF PATIENTS WITH LOW RISK OF STROKE (CHA_2DS_2-VASC SCORE 0, OR 1 IN FEMALES)

	Hazard Ratio (95% Confidence Interval)	**p**
	Patients with no risk factor as reference	
No risk factor (n=1078)	1	-
Heart Failure (n=377)	3.04 (1.99-4.63)	<0.0001
Hypertension (n=136)	1.48 (0.72-3.07)	0.29
Age 65-74 (n=484)	2.40 (1.56-3.69)	<0.0001
Diabetes (n=41)	2.23 (0.69-7.24)	0.18
Vascular disease (n=61)	2.11 (0.94-4.71)	0.07

TABLE 5. UNIVARIATE AND MULTIVARIATE ANALYSIS OF SECONDARY ENDPOINT (DEATH, STROKE , SYSTEMIC THROMBOEMBOLISM OR MAJOR BLEEDING) PREDICTORS IN THE POPULATION OF AF PATIENTS WITH LOW RISK OF STROKE (CHA_2DS_2-VASC SCORE 0, OR 1 IN FEMALES) OR WITH 1 ADDITIONAL RISK FACTOR (CHA_2DS_2-VASC SCORE 1 IN MALES, 2 IN FEMALES)

	Univariate analysis		**Multivariate analysis**	
	Hazard Ratio (95% Confidence Interval)	**p**	**Hazard Ratio (95% Confidence Interval)**	**p**
Age	1.03 (1.02-1.04)	<0.0001	1.04 (1.03-1.06)	<0.0001
Female gender	0.81 (0.60-1.10)	0.17	0.75 (0.53-1.05)	0.09
Heart Failure	1.93 (1.45-2.57)	<0.0001	2.70 (1.90-3.85)	<0.0001
Hypertension	1.11 (0.67-1.82)	0.68	1.64 (0.93-2.87)	0.08
Diabetes	1.14 (0.42-3.08)	0.79	2.38 (0.86-6.54)	0.09
Vascular disease	1.19 (0.63-2.24)	0.59	1.38 (0.62-3.05)	0.43
Coronary artery disease	1.46 (1.01-2.11)	0.05	1.48 (0.92-2.36)	0.11
Valvular disease	5.41 (3.01-9.62)	<0.0001	1.65 (1.14-2.39)	0.01
Renal insufficiency	1.72 (1.10-2.70)	0.02	4.93 (2.45-9.90)	<0.0001
Chronic pulmonary disease	1.06 (0.80-1.41)	0.69	1.57 (0.99-2.50)	0.06
Permanent atrial fibrillation	1.01 (0.76-1.32)	0.97	0.84 (0.62-1.15)	0.28
Oral anticoagulant treatment	0.88 (0.63-1.23)	0.45	0.67 (0.49-0.92)	0.01
Antiplatelet treatment	1.03 (1.02-1.04)	<0.0001	0.81 (0.56-1.18)	0.27




Event free
1,0
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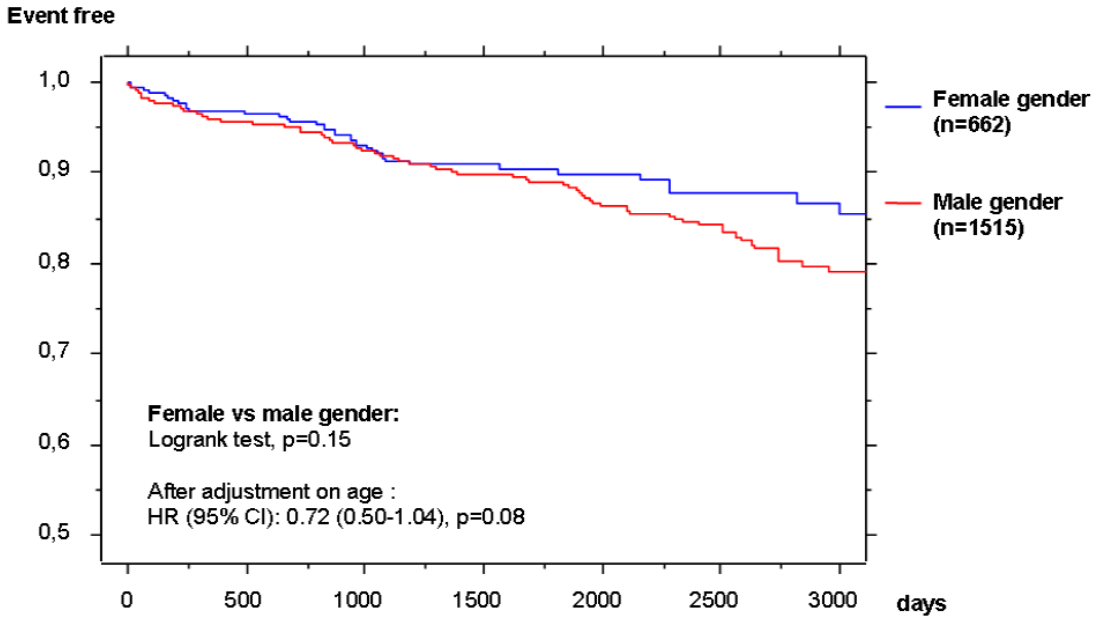
days
(0)
(C)
(H)
(A)
(D)
(V)
Logrank test:
p<0.0001 for the 6 groups of patients
p=0.34 for the 5 groups of patients with 1 risk factor


Event free
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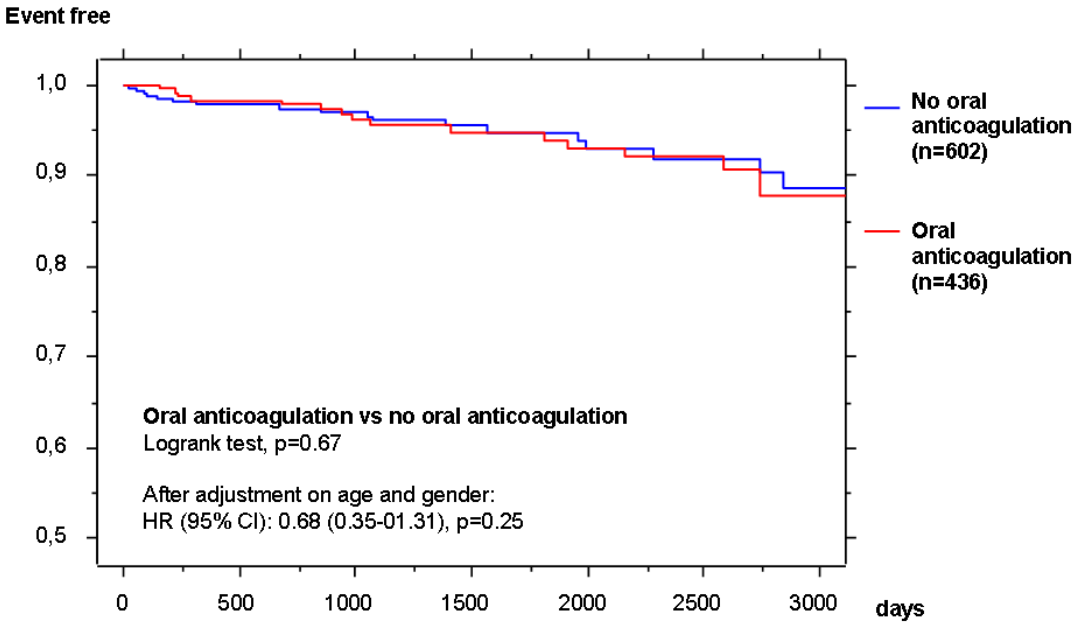
days
Female gender
(n=662)
Male gender
(n=1515)
Female vs male gender:
Logrank test, p=0.15
After adjustment on age :
HR (95% CI): 0.72 (0.50-1.04), p=0.08


Event free
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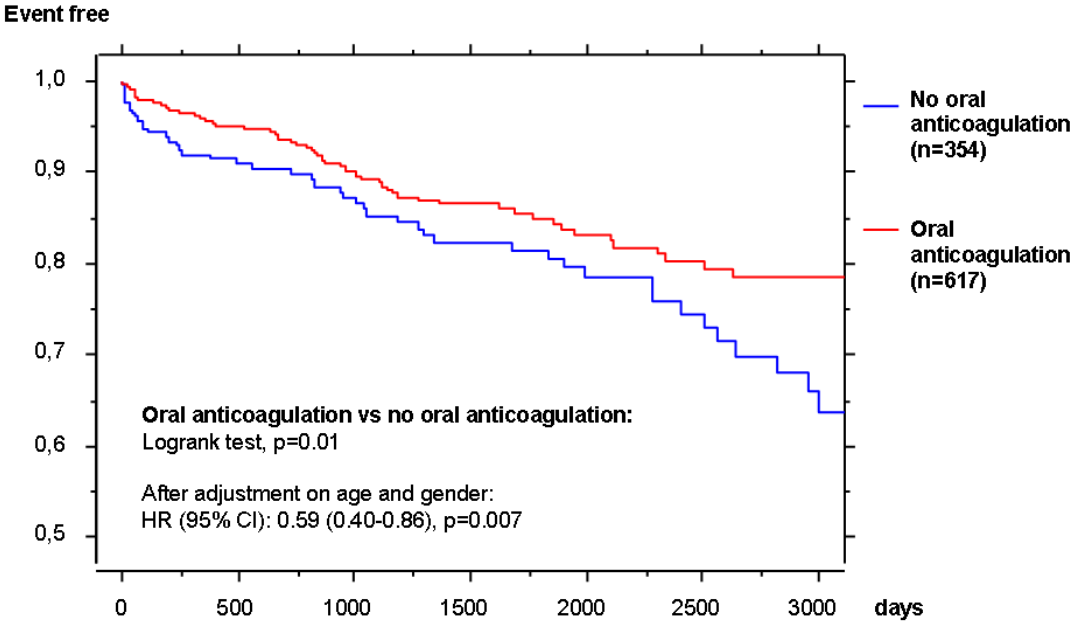
days
No oral anticoagulation (n=602)
Oral anticoagulation (n=436)
Oral anticoagulation vs no oral anticoagulation
Logrank test, p=0.67
After adjustment on age and gender:
HR (95% CI): 0.68 (0.35-01.31), p=0.25


Event free
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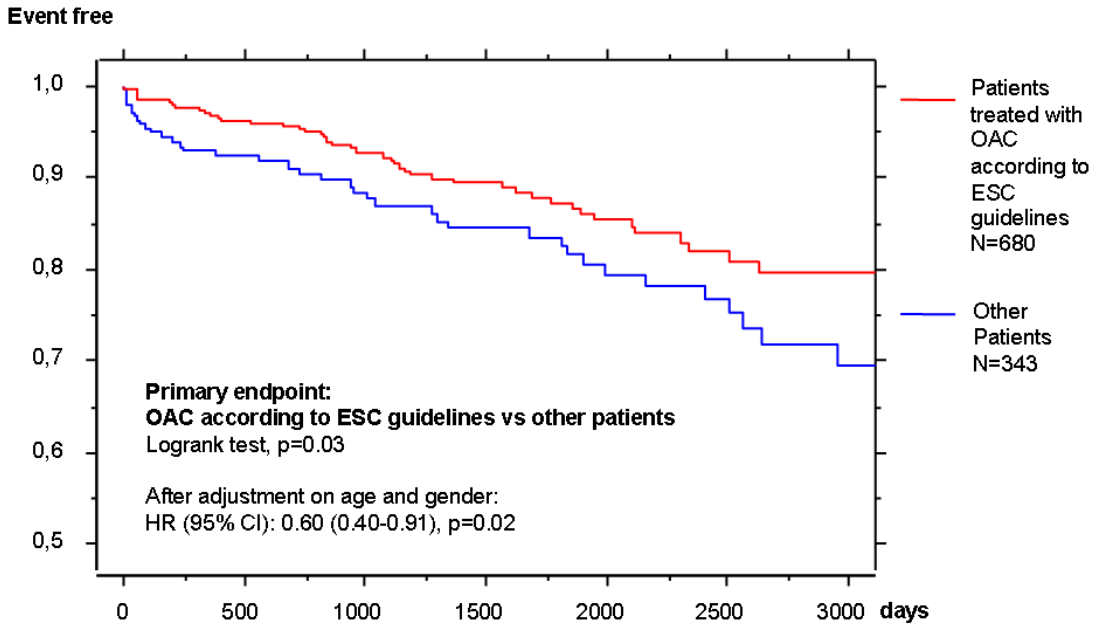
days
No oral anticoagulation (n=354)
Oral anticoagulation (n=617)
Oral anticoagulation vs no oral anticoagulation:
Logrank test, p=0.01
After adjustment on age and gender:
HR (95% CI): 0.59 (0.40-0.86), p=0.007


Event free
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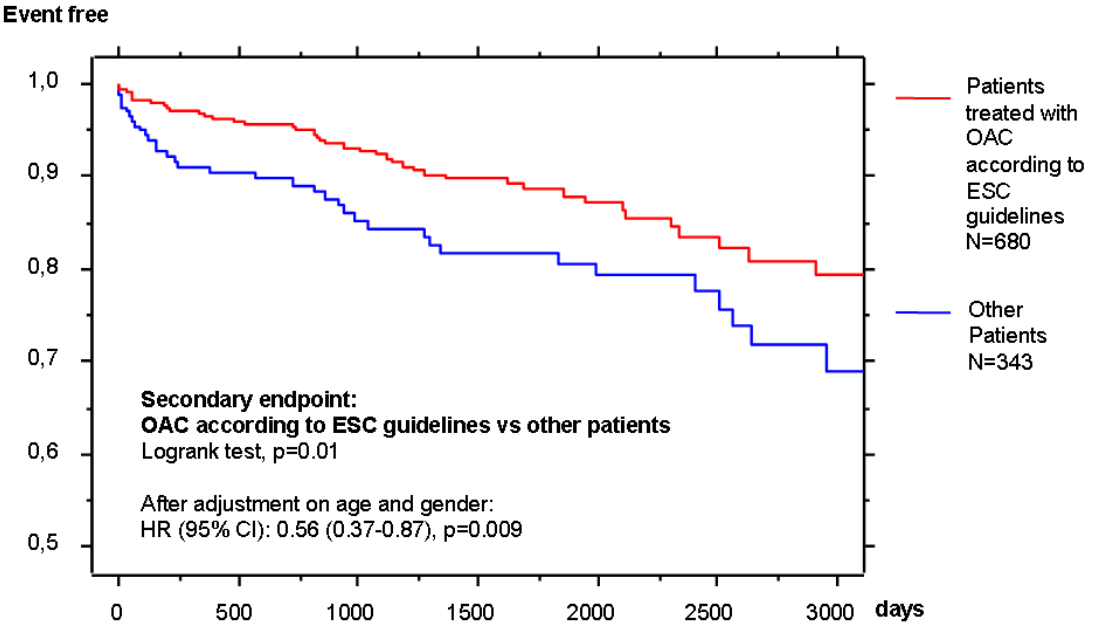
days
Primary endpoint:
OAC according to ESC guidelines vs other patients
Logrank test, p=0.03
After adjustment on age and gender:
HR (95% CI): 0.60 (0.40-0.91), p=0.02
Patients treated with OAC according to ESC guidelines N=680
Other Patients N=343


Event free
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0,8
0,7
0,6
0,5
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3000
days
Secondary endpoint:
OAC according to ESC guidelines vs other patients
Logrank test, p=0.01
After adjustment on age and gender:
HR (95% CI): 0.56 (0.37-0.87), p=0.009
Patients treated with OAC according to ESC guidelines N=680
Other Patients N=343

CHEST™ Online Supplement

e-Table 1. International Classification of Disease 10 (ICD-10) codes

Comorbidity or medical history	Existing diagnoses between 1 January 2007 and 31 December 2011
AF management care	I48
AF symptoms	
Tachycardia	R000
Chest pain	R072, R073, R074
Palpitations	R002
Strokes	
Ischaemic stroke	I63, I66, I67
Stroke, unspecified	I64
Haemorrhagic stroke	I60–I62, I69
Transient ischaemic attack	G45
Systemic embolism	I74.2–I74.9
Haemorrhages	
Intracranial bleeding	S064–S066
Gastric/duodenal ulcer	K25–K28 (subcodes 0–2 and 4–6 only)
Any severe bleeding	I850, I983, K625, K922
Ischaemic heart disease	I20–I25
Heart failure	I50, I110, I130, I132, I131, I139
Including dyspnoea	R060
Cardiac dysrhythmia	I47, I490–I493
Abnormal cardiac conduction	I44, I45, I494, I495, Z450, Z950
Valvular disease	I05–I091, I33–I39, Q22, Q23
Hypertension	I10–I15
Diabetes mellitus	E10–E14
Vascular diseases	
Myocardial infarction	I21, I252
Peripheral arterial disease	I70–I73
Occlusions	I65, I77
Obesity	E65–E66
Abnormal renal function	N17–N19 (+N28) codes for renal insufficiency, transplantation (Z940, T861) and dialysis (Z49, Z992), E102, I12, I13
Liver disease	K70–K77, procedures for liver transplantation or resection
Dyslipidaemia	E78
Thyroid disease	E00–E07
Anaemia	D50–D64
Platelet or coagulation defect	D65–D69
Lung disease	J40–J70, J961
Including emphysema and chronic obstructive pulmonary disease	J43, J44
Alcohol-related diagnoses	E244, F10, G312, G621, G721, I426, K292, K70, K860, O354, P043, Q860, T51, Y90, Y91, Z502, Z714
Dementia	F00–F03
Accidental falls	W00–W19, R26
Cancer	Entire C-series

AF, atrial fibrillation.